IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Reissue Patent Application of:

William Stern	Confirmation No.: 8408
Serial No.: 10/774,358	Group Art Unit: 1616
Filed: February 5, 2004	Examiner: Mina Haghighatian
Original Patent No.: 6,440,392	
Issued: August 27, 2002	
For: NASAL CALCITONIN FORMULATION	

Mail Stop Reissue
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

FOURTH DECLARATION OF INVENTOR
WILLIAM STERN UNDER 37 CFR §1.132

I, William Stern, hereby declare that:

1. My background and relationship to the present patent application, and to its owner, Unigene, are as stated in paragraphs 1-3 of my Second Declaration of Inventor William Stern Under 37 CFR §1.132 executed by me on September 7, 2007, and previously filed.

2. This declaration is for the purpose of further explaining specification support, and supporting experimental data, for amendments made during reissue proceedings, and values stated in the specification, which I understand to be the subject of inquiries from quality review personnel in the U.S. Patent and Trademark Office.

3. All documents attached as exhibits hereto are either (1) documents kept in the ordinary course of business at Unigene which report the results of experimentation done by me, or by others under my supervision, or (2) tabulations or summaries of such documents or experimentation. Further details of each attachment are provided *infra*.

Support For Amendments to Table 2 of the specification :

4. Attached as **EXHIBIT A** hereto is a summary of data compiled from records kept by Unigene in the ordinary course of business. Some representative laboratory notebook pages and underlying data for the formulations whose performance is summarized in **EXHIBIT A** is attached hereto as **EXHIBIT B** (discussed in more detail in paragraph 6 *infra).* **EXHIBIT A** documents the basis for the data in Table 1 of the specification, and of selected Table 2 data, namely the Table 2 entries for the phenylethyl alcohol/benzyl alcohol- containing sCT formulations. In **EXHIBIT A**, Reference code "BA" followed by three digits refers to study number; the next letter refers to formulation (which in the laboratory notebooks is designated by roman numeral); the next number refers to rat identification (which in laboratory notebooks is designated by color). Cmax refers to maximum sCT concentration; %F refers to bioavailability . The concentration number given in "mM" is for citric acid content. The notebook references for the data in **EXHIBIT A** are YMY 515:005, YMY 515:006, YMY 515:007 and YMY 515:008. A previously submitted version of **EXHIBIT A** (Exhibit C to my Third Declaration filed in October, 2007) had mentioned notebooks YMY 515:006, YMY 515:007, but not YMY 515:005 and YMY 515:008, which are also relevant and are now cited in **EXHIBIT A**.

5. Referring to **EXHIBIT A**, Table 2's amended bioavailability and maximum plasma concentration of salmon calcitonin active ingredient (sCT) for the phenylethyl alcohol/benzyl alcohol- containing sCT formulations is derived from the rat data reported in the first three columns of **EXHIBIT A** . The formulations tested in those first three columns are the ones whose citric acid concentration is zero. (Concentrations at the top of **EXHIBIT A** are citric acid concentrations). Unlike Table 1, whose purpose is to compare results at different citric acid concentrations, Table 2 seeks to compare the results using a variety of preservatives (or no preservatives). The data from **EXHIBIT A** where citric acid concentration is zero best isolates

any such preservative effects because citric acid effects of the invention are absent from this data. The other comparative formulations whose performance is Table 2 (e.g. formulations with a different preservative (or no preservative) are also formulations having zero citric acid. The average (and standard deviations) for bioavailability and maximum plasma sCT reported for the rats that received the relevant phenylethyl alcohol/benzyl alcohol- containing sCT formulations are calculated at the bottom of columns 1,2, and 3 of **EXHIBIT A**, and are identical to the values now stated in amended Table 2.

Support For the sCT formulations tested in Table 1 having a pH of 3.7:

6. Attached hereto as **EXHIBIT B** are laboratory notebook Pages 283 and 284 of Unigene notebook YMY 515:005; pages 49 and 64 of Unigene notebook YMY 515:006; pages 1, 2, 60, 240 and 241 of Unigene notebook YMY 515:007; and pages 11 and 15 of Unigene notebook YMY 515:008 showing formulation details for sCT formulations administered to rats in studies BA 285, 289, 290, 301, 303, 311, 312 and 313. Of these, all but study BA 285 were among the studies used to generate the data in **EXHIBIT A**. Details of study BA 285 are attached because several other studies use the formulations of study BA 285.

7. In the specification, pH values from the underlying data are rounded to a single decimal place. The two decimal place figures shown in the lab notebook pages approach the limits of detection. Additionally, to an accuracy of two decimal places, the formulations are likely undergoing some minor pH drift even over short periods of time. The target pH for all formulations whose performance is evaluated in Table 1 was 3.7, as was the average value measured (rounded to a single decimal place), although a very small number of individual measurements to two decimal places fell slightly outside the range that rounds to 3.7. Referring to **EXHIBIT B**, the bottom of page 284 of notebook YMY 515:005, at column 9, shows that the formulations of BA285 had a pH of 3.7 (when rounded to a single decimal place). Study BA289 used those same formulations (see the notation "same formulation as BA285" near the bottom of page 49 of notebook YMY 515:006). Likewise, study BA290 used the same

formulations as study 289 (see the notation near the bottom of page 64 notebook YMY 515:006). Formulation III of study BA311 - - the only formulation from study BA311 whose performance is reported at Exhibit A (as BA311C1 and BA311C2) and included in the data of specification Table 1 - - has components identical to that of formulation II of study to BA285 whose pH was measured at 3.69. (Compare pages 240 and 241 of notebook YMY 515:007 to page 284 of notebook YMY 515:005). Studies BA312 and BA313 used the same formulation as did Study BA311. (See the bottom of pages 11 and 15 of notebook YMY 515:008). Pages 1, 2 and 60 of notebook YMY 515:007 show a target pH for studies BA301 and BA303 of 3.7. See page 2, column 8 (which reports pH for the formulations I, II and III on page 1 related to study BA301), and page 60 near the bottom (relating to pH of formulations used in study BA303).

8. The purpose of the studies discussed in the foregoing paragraph 7 was to measure the effect of various citric acid concentrations independent of other parameters, which parameters applicant therefore sought to hold constant (for example, by targeting a relatively constant pH near 3.7 as shown in **EXHIBIT B**). The bioavailability and maximum sCT values from each rat study discussed in paragraph 7 hereof, and other similar rat studies, were then tabulated in **EXHIBIT A** . The bottom two lines of **EXHIBIT A** show average bioavailability (%f) and average maximum sCT concentration (Cmax), and standard deviations thereof, for all of these rat studies. These averages and standard deviations are then reported in Table 1 of the patent specification.

Support For Table 3 showing test data for sCT formulations having pH 3.8:

9. Attached hereto as **EXHIBIT C** are pages 205 and 206 of laboratory notebook LMF 515:030. Page 205, rows 20-23, columns 1-8 show the content, and pH, of all but one of the formulations tested for stability in Table 3 of the patent specification. (The exception, where citric acid is zero, is discussed *infra*). As may be seen in column 8, rows 20-23, the target pH for these formulations is 3.8. A single pH measurement at column 8, row 20 was measured at 3.88. However, as also noted in paragraph 7, pH values measured to two decimal place figures approach the limits of detection. Additionally, to an accuracy of two decimal places, the

formulations are likely undergoing some minor pH drift even over short periods of time. The average pH measured on relevant lines 20-23 of page 205 was 3.8 (rounded to a single decimal place). The purpose of these studies was to measure the effect of various citric acid concentrations independent of other parameters which applicant therefore sought to hold constant (for example, by targeting a relatively constant pH near 3.8 as shown in **EXHIBIT C**). With respect to the formulation wherein the citric acid content was zero, page 205, at the far right-hand side shows that several formulations wherein the pH was well above the 3.8 target were "tossed." At line 30, one such formulation is "kept" and then, on page 206, has its pH further adjusted to the desired 3.8 pH target. (Both successful and unsuccessful adjustments are shown on page 206).

Support For Reciting 0.85% sodium chloride in Example 3:

10. The same portion of **EXHIBIT C** discussed in the prior paragraph supports 0.85% sodium chloride (NaCl). The content of formulations tested for stability in Table 3 of the patent specification included a mixture set forth in **EXHIBIT C**, page 205, column 5. The last ingredient of that mixture is stated as "1.7% NaCl" which is then diluted 2:1 when the 2.5 ml of the column 5 mixture is diluted with another 2.5 ml of other ingredients of the final formulations. See the sum of other ingredients added in columns 3, 4, and 7. (Note that Specification Table 3 does not include data for the very different benzalkonium chloride formulation set forth on line 24 of page 205, which line should be disregarded for that reason).

Support For Reciting pH 3.5-3.9 in claim 13:

11. Attached hereto as **EXHIBIT D** are pages 046, 132 and 133 of Unigene laboratory notebook ETM:002. The 3.5-3.9 pH range stated in claim 13 is derived from applicant's preferred range stated at **Column 3, line 12 and also original claim 13 of the specification**, which is in turn even narrower than the broader range that is supported by **EXHIBIT D**. As discussed in more detail in paragraphs 12 and 13 *infra*, **EXHIBIT D** shows good results using a variety of pH values from 3.3 to 4.1, easily predicting good results within the stated 3.5-3.9 range of claim 13.

12. Specifically, **EXHIBIT D**, page 046 shows the content of a variety of different salmon calcitonin formulations. The Formulations numbered 3-10 all have citric acid added at a concentration within the critical 10-25 mM range recited in claim 13 (specifically 10 mM). Formulations numbered 11-18 all have citric acid added at a concentration outside the critical 10-25 mM range recited in claim 13, (specifically 100 mM). A variety of pH values are represented among formulations 3-18. **EXHIBIT D**, page 132, shows the stability of the various formulations under different storage conditions. The final column of page 132 shows percent of active ingredient sCT remaining after one month at room temperature (25 C). **EXHIBIT D**, page 133, shows similar data under more extreme storage conditions. The final column of page 133 shows percent of active ingredient sCT remaining after one month at 50 C. These data show almost no degradation at room temperature for formulations whose pH ranged from as low as 3.3 to as high as 4.1 as long as those formulations included citric acid within applicant's recited range. See **EXHIBIT D**, page 132, final column, for stability of formulations 3, 4, 5, 6, 7, and 8. Even at the more severe storage conditions set forth on **EXHIBIT D**, page 133, the data show best stability for formulations whose pH ranged from as low as 3.3 to as high as 4.1 for formulations that included citric acid within applicant's recited range. See **EXHIBIT D**, page 133, final column, for stability of formulations 3, 4, 5, 6, 7, and 8.

13. Additionally the advantage applicant has discovered for holding citric acid levels within the 10-25mM range appears in the **EXHIBIT D** data at every pH tested from pH 3.3 through pH 4.1, easily encompassing the claim 13 range of 3.5-3.9. For example, formulations 4 and 12, both having pH of 3.3 are alike in all respects except that formulation 4 has an amount of citric acid within the scope of claim 13 and formulation 12 has an amount of citric acid outside the scope of claim 13. **EXHIBIT D**, page 133, final column, shows that formulation 4 outperformed formulation 12. Likewise, at pH 3.7, formulation 6 (citric acid concentration within the scope of claim 13) outperformed formulation 14 (citric acid concentration outside the scope of claim 13). And at pH 4.1, formulation 8 (citric acid concentration within the scope of claim 13) outperformed formulation 16 (citric acid concentration outside the scope of claim 13).

Support for claim 13's recitation of aggregate bioavailability enhancing agent

14. The bioavailability enhancing agent in claim 13 is defined in claim 13 itself. That claim 13 definition does not include any compound other than citric acid or citric acid salt, both of which are discussed in the original specification for their contribution to bioavailability. See, for example, column 2, lines 21-31 of the specification, example 1 and table 1.

15. It is necessarily the aggregate amount of the agent (whether added in the form of citric acid , citric acid salt, or a mixture) whose effects are reported in Tables 1 and 3. That is because citric acid buffered to the pH range recited in claim 13 (pH 3.5-3.9) or used in Table 1 (pH 3.7) or Table 3 (pH 3.8) always exists as a particular mixture of citric acid and citric acid salt at a given pH, regardless of whether citric acid, citric acid salt or a mixture thereof was originally provided. The Henderson-Hasselbach equation requires this result. For example, citric acid buffered at a pH above 3.5, at all of the citric acid concentrations of 10 mM or higher shown in Tables 1 and 3, is necessarily a combination of citric acid and citric acid salt, as dictated by a version of the Henderson-Hasselbach equation for buffers with two pK's as noted below:

$$pH = ((pK1 + pK2) + \log (salt/acid))/2$$

Although citric acid has three pKs, pK3(6.19) has little if any effect on buffering properties of the buffering system at pH 3.5-3.9, and is therefore ignored in the foregoing equation to make the math simpler. In all of the concentrations of citric acid reported in Tables 1 and 3 that are 10mM or higher, the pH would have been considerably lower than 3.5 if the citric acid had not been buffered by the presence of a salt. For example, had the pH been raised to 3.5 or higher by a mere addition of water, the resulting citric acid concentration would be significantly below 10mM. The Henderson-Hasselbach equation dictates that a 10mM (or higher) aqueous citric acid exists as a mixture of citric acid and citric acid salt at a pH of 3.5 or higher. This does not necessarily mean that salt has been added. A base could be used to raise pH to 3.5 or higher. However, the addition of a base would cause the formation of salt in accordance with the above Henderson-Hasselbach equation. In other words, regardless of whether pH is raised to 3.5 or higher by using

a base, or by using a salt, salt will necessarily be present either (1) because salt was included during preparation, or (2) because salt was formed when base was included during preparation.

16. In view of the foregoing, the effect on bioavailability and stability that is reported in Tables 1 and 3 of the specification, respectively, is provided in solutions that necessarily include a combination of both citric acid and citric acid salt.

17. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

7/25/08
Date

William Stern
William Stern

EXHIBIT A

Reference code: BA followed by 3digits refers to study #, letter refers to formulation within notebook is designated by Roman numeral), # refers to rat ID (which in notebook is designated by color). Cmax refers to maximum sCT concentration. %F refers to bioavailability. Notebook reference for data below: YMY 515:005, YMY 515:006, YMY 515:007 and YMY 515:008

0mM				10mM				25mM				50mM				100mM		
Reference#	Cmax	%F		Reference#	Cmax	%F		Reference#	Cmax	%F		Reference#	Cmax	%F		Reference#	Cmax	%F
BA289B1	1.99	1.06		BA289C1	3.40	2.67		BA301B1	3.12	2.85		BA325A1	6.84	[illegible]		BA301C1	10.50	10.10
BA289B2	1.14	1.09		BA289C2	2.10	1.89		BA301B2	8.27	7.69		BA325A2	6.85	[illegible]		BA301C2	10.78	13.51
BA289B3	0.91	0.69		BA289C3	2.55	2.44		BA302B1	2.96	3.62		BA325A3	5.54	[illegible]		BA301C3	14.34	12.26
BA290B1	0.62	0.78		BA290C1	1.52	1.37		BA302B2	6.23	6.61		BA326A1	7.90	[illegible]		BA302C1	14.23	13.77
BA290B2	1.33	1.05		BA290C2	3.42	3.32		BA302B3	3.14	2.65		BA326A2	6.17	[illegible]		BA302C2	8.35	9.02
BA290B3	0.62	0.67		BA290C3	3.28	2.99		BA306B1	6.07	4.97		BA326A3	4.02	[illegible]		BA302C3	17.29	18.03
BA311C1	1.04	0.96		BA303A1	4.98	5.91		BA306B2	3.91	3.13						BA306C1	20.11	18.37
BA311C2	1.60	1.60		BA303A2	3.03	3.41		BA306B3	7.24	8.59						BA306C2	8.76	10.12
BA312C1	2.72	2.75		BA303A3	5.58	4.66		BA319C1	8.09	[illegible]						BA306C3	12.44	15.10
BA312C2	2.85	2.86		BA304C1	2.45	2.85		BA319C2	8.32	8.79								
BA313C1	1.63	1.58		BA304C2	3.34	3.89		BA320C1	2.91	3.46								
BA313C2	0.53	0.61		BA304C3	2.42	3.00		BA320C2	[illegible]	8.84								
				BA305C1	5.55	5.20		BA321C1	9.05	10.73								
				BA305C2	2.12	2.53		BA321C2	7.07	8.84								
				BA305C3	1.30	1.09	[redacted]											
				BA307A1	4.85	4.89												
				BA307A2	4.26	4.76												
				BA307A3	4.51	4.51												
				BA308B1	4.75	3.66												
				BA308B2	4.80	5.10												
				BA308B3	3.36	3.68												
				BA309B1	6.37	5.97												
				BA309B2	6.69	5.36												
				BA314A1	3.46	3.81												
				BA314A2	2.02	[illegible]												
				BA315A1	4.33	4.00												
				BA315A2	2.57	2.09												
				BA316A1	2.79	2.81												
				BA316A2	2.41	2.51												
				BA319B1	5.38	5.86												
				BA319B2	1.86	1.98												
				BA320B1	[illegible]	4.94												
				BA320B2	2.31	2.22												
				BA321B1	4.77	5.15												
				BA321B2	2.48	2.48												
AVG	1.42	1.31			[illegible]	3.57			[illegible]	[illegible]			6.05	[illegible]			12.98	13.36
SDEV	0.78	0.77			[illegible]	1.39			2.30	2.93			1.30	[illegible]			3.93	3.38

EXHIBIT B

UNIGENE LABORATORIES, INC.
BLOOD SAMPLE LOG SHEETS

Project Description: BA 285 Date: 4/13/99

Analyst: Yuri, WS

Time (minutes)	0	5	15	30	60	120
Animal I.D.						
I Wh/W	0	5	15	30	60	120
I Ye/W	2	7	17	32	62	122
I Re/W	4	9	19	34	64	124
II Pe/W	6	11	21	36	66	126
II Gr/W	8	13	23	38	68	128
II Bl/W	10	15	25	40	70	130
III Or/W	12	17	27	42	72	132
III Blue/W	14	19	29	44	74	134
III Tan/W	16	21	31	46	76	136

Comments: t=0 administered dose

I 50 µl (200 mg/ml) sCT in 0.0005 N HCl + 0.85% NaCl in 0.02% Benzyldimethyl Cl

II 50 µl (200 mg/ml) sCT in 0.0005 N HCl + 0.85% NaCl in 0.2% BEtOH + 0.5% BzOH + 0.1% Tween 80

III 50 µl (200 mg/ml) sCT in 10 mM citric acid + 0.85% NaCl in 0.2% BEtOH + 0.5% BzOH + 0.1% Tween 80.

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4/13/99 BA285

phenyl ethyl OH + 1.02 g

benzyl OH + 2.49 g
Tween 80 + 0.52 g
H_2O + 246.99 g

for stock 2

Stock 2 = .4% phenylethyl OH
1% benzyl alcohol
.2% Tween 80
1.7% NaCl

NaCl + 4.26 g

for stock 2

benzalkonium Cl
+ 0.24 g
H_2O + 600.01 g

NaCl + 10.21 g
for stock 1

stock 1 = .04% benzalkonium Cl
1.7% NaCl

	stock ① 1.7% NaCl in .04% BZA	stock ② 1.7% NaCl in .4% PEA, 1% BA, .2% Tween 80		.1N HCl	[illegible] pH 3.64	ART 10 mg/ml	H_2O	pH
I	1			10µl		40µl	950µl	3.65
II		1		10µl		↓	950µl	3.69
III		1			200µl	↓	750µl	3.73

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UNIGENE LABORATORIES, INC.
BLOOD SAMPLE LOG SHEETS

Project Description: BA 289 Date: 4/22/99

Analyst: yrj, VS

Time (minutes)	0	~~5~~ 30	~~25~~ 60	~~35~~ 90	~~55~~ 120	~~120~~ 150
Animal I.D.						
Bl/M	0	30	60	90	120	150
Yl/W	2	32	62	92	122	152
Re/W	4	34	64	94	124	154
Pu/W	6	36	66	96	126	156
Gr/W	8	38	68	98	128	158
Bl/W	10	40	70	100	130	160
Or/W	12	42	72	102	132	162
Blu/W	14	44	74	104	134	164
Tan/W	16	46	76	106	136	166

I
II
III

yrj 4/22/99

Comments: administered dose at t=0, 30", 60", 90"

25ml I (4/13/99) I 4x 25µl (200µg/ml) sCT in 0.0005M HCl + 0.02% Benzalkonium Cl + 0.85% NaCl

25ml II (4/13/99) II " " in 0.0005M HCl + 0.2% Acetate + 0.85% NaCl

25ml III (4/13/99) III " 10mM citric acid + " yrj 4/22/99

* same formulation as BA 285 (prepared 4/13/99)

+20µg dose sCT

(reference: yrj 315:005 page 283-284) yrj 4/23/99

yrj 4/22/99

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INITIALS

UNIGENE LABORATORIES, INC.
BLOOD SAMPLE LOG SHEETS

Project Description: BA290

Date: 4/23/99

Analyst: YJ / WS

Time (minutes)	0 *	30 *	60 *	90 *	120	150
Animal I.D.						
I Wh/W	0	30	60	90	120	150
I Yel/W	2	32	62	92	122	152
I Red/W	4	34	64	94	124	154
II Pu/W	6	36	66	96	126	156
II Gr/W	8	38	68	98	128	158
II Bl/W	10	40	70	100	130	160
III Or/W	12	42	72	102	132	162
III Blue/W	14	44	74	104	134	164
III Tan/W	16	46	76	106	136	166

Comments: administered dose at t = 0, 30', 60', 90'

I 4 X 0.025 ml (200 µg/ml) sCT in 0.005 N HCl + 0.02% Benzalkonium Cl + 0.85% NaCl

II " in " + 0.2% [illegible] + 0.5% [illegible] + 0.1% Tween 80 + *

III " in 10 mM citric acid + " + " + " + *

* same formulation as BA289 (prepared 4/13/99) (reference page 49 YJ 4/23/99)

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UNIGENE LABORATORIES, INC.
BLOOD SAMPLE LOG SHEETS

Project Description: BA301 Date: 5/19/99

Analyst: yuej, ws

	Time (minutes)	0	30	60	90	120	150
	Animal I.D.						
I	Wh/w	0	30	60	90	120	150
	Ye/w	2	32	62	92	122	152
	Re/w	4	34	64	94	124	154
II	Pu/w	6	36	66	96	126	156
	Gr/w	8	38	68	98	Died 128	~~158~~
	Bl/w	10	40	70	100	130	160
III	Or/w	12	42	72	102	132	162
	Blue/w	14	44	74	104	134	164
	Tan/w	16	46	76	106	136	166

Comments: t=0, 30, 60, 90 administered dose

I 4X25μl (200μg/ml) + 0.0005NHCl + 0.02%Benzalkonium Cl + 0.85%NaCl

II 4X25μl (200μg/ml) + 25mM Citric acid (pH=3.66) + 0.2%PEtOH + 0.5%BzOH + 0.1%Tween80 + 0.85% NaCl

III 4X25μl (200μg/ml) + 100mM citric acid + 0.2%PEtOH + 0.5%BzOH + 0.1% Tween80 + 0.85% NaCl

* 20μg dose/rat.

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PAGE # 1

5/11/99 [illegible] Preparation of solns for BA 301

	1	2	3	4	5	6	7	8
3						(10mg/ml)		
4		stock 1	stock 2	500mM CA pH 3.66	.1N HCl	BCT 100mg/ml	H_2O	pH
5	I	1ml			10ul	40ul	950ul	3.68
6	II		1ml	100ul		↓	860ul	3.72
7	III		1ml	400ul		↓	560ul	3.69

stock 1 = 1% NaCl in .01% benzalkonium Cl

stock 2 = 1% NaCl in .4% phenylethyl alcohol, 1% benzyl OH, .2% Tween 80

EFFICIENCY LINE • 22-203

5/11/99 [signature]

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UNIGENE LABORATORIES, INC.
BLOOD SAMPLE LOG SHEETS

Project Description: BA 303 Date: 5/25/99

Analyst: Yyyy uuu

Time (minutes)	0	30	60	90	120	150
Animal I.D.						
I Wh/w	0	30	60	90	120	150
Ye/w	2	32	62	92	122	152
Re/w	4	34	64	94	124	154
II Pu/w	6	36	66	96	DUP 126	156
Gr/w	8	38	68	98	128	158
Bl/w	10	40	70	100	130	160
III Or/w	12	42	72	102	132	162
Bk-/w	14	44	74	104	134	164
Tan/w	16	46	76	106	136	166

Comments: all contain .5% propyl or, .2% phenylethyl alc, .1% Tween 80

I ACT (complete) in 10mM citric acid pH 3.73 (#8) (5/18/99)

II ACT (complete) in 10mM phosphate pH 3.20 (#N) (5/18/99)

III ACT (complete) in 10mM phosphate pH 3.28 (#P) (5/18/99)

* all 4x25µl at: 0, 30, 60, 90 / 1X 1X 1X 1X

add 3ml .1M HCl to ~1.5ml sample to reduce pH from 3.91 to 3.77

UNIGENE LABORATORIES, INC.
BLOOD SAMPLE LOG SHEETS

Project Description: BA311 Date: 6/22/99

Analyst: [illegible] / WS

	Time (minutes)	0	30	60	90	120	150
	Animal I.D.						
II	Wh/W	0	30	60	90	120	150
II	Yel/W	2	32	62	92	122	152
III	Re/W	4	34	64	94	124	154
III	Pu/W	6	36	66	96	126	156
IV	Gr/W	8	38	68	98	128	158
IV	Bl/W	10	40	70	100	130	160
I	Or/W	12	42	72	102	132	162
I	Blue/W	14	44	74	104	134	164
I	Tan/W	16	46	76	106	136	166

Comments: t = 0, 30', 60', 90' → administered dose

I 4x25 μl (200 μg/ml sCT) + 0.0005 N HCl + 0.85% NaCl

II 4x25 μl (200 μg/ml sCT) + 0.0005 N HCl + 0.27% MeP + 0.04% PrP + 0.83% NaCl

III 4x25 μl (200 μg/ml sCT) + 0.0005 N HCl + 0.2% ϕEtOH + 0.5% BzOH + 0.1% Tween 80 + 0.85% NaCl

IV 4x25 μl (200 μg/ml sCT) + 0.0005 N HCl + 0.2% ϕEtOH + 1% BzOH + 0.1% Tween 80 + 0.85% NaCl

6/22/99

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[redacted]

6/22/49 VJ

	1	2	3	4	5	6	7	8	9
1									
2									
3									
4									
5									
6	I								
7	II								
8	III								
9	IV								
10									
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EFFICIENCY LINES 22-209

6/22/49

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INITIALS [redacted]

UNIGENE LABORATORIES, INC.
BLOOD SAMPLE LOG SHEETS

Project Description: BA312

Date: 6/24/99

Analyst: YJ, WS

Time (minutes)	0	30	60	90	120	150
Animal I.D.						
II Wh/w	0	30	60	90	120	150
Ye/w	2	32	62	92	122	152
III Re/w	4	34	64	94	124	154
Pu/w	6	36	66	96	126	156
IV Gr/w	8	38	68	98	128	158
Bl/w	10	40	70	100	130	160
I Or/w	12	42	72	102	132	162
Blu/w	14	44	74	104	134	164
Tan/w	16	46	76	106	136	166

Comments: t_0 = 0, 30, 60, 90" - administered dose

I 4X25µl (200µg/ml sCT) + 0.0005N HCl + 0.85% NaCl

II 4X25µl (200µg/ml sCT) + 0.0005N HCl + 0.2% NaP + 0.04% PoP + 0.83% NaCl

III 4X25µl (200µg/ml sCT) + 0.0005N HCl + 0.2% EtOH + 0.6% BzOH + 0.1% Tween 80 + 0.85% NaCl

IV 4X25µl (200µg/ml sCT) + 0.0005N HCl + 0.2% EtOH + 1% BzOH + 0.1% Tween 80 + 0.85% NaCl

* same formulation as experiment on BA311

(YJ 5758/7 p. 240-241

YJ 6/24/99

NOTEBOOK # 5758/7
PAGE # 240-241
DATE 6/24/99
INITIALS YJ

YJ 6/25/99

UNIGENE LABORATORIES, INC.
BLOOD SAMPLE LOG SHEETS

Project Description: BA313 Date: 6/25/99

Analyst: [illegible], WS

Time (minutes)	0	30	60	90	120	150
Animal I.D.						
I Wh/w	0	30	60	90	120	150
I Y/w	2	32	62	92	122	152
III Re/w	4	34	64	94	124	154
III Pu/w	6	36	66	96	126	156
IV Gr/w	8	38	68	98	128	158
IV Bl/w	10	40	70	100	130	160
II Or/w	12	42	72	102	132	162
II Blue/w	14	44	74	104	134	164
II Tan/w	16	46	76	106	136	166

Comments: t=0, 30', 60', 90' — administered dose

I 4x25 µl (2 µg/kg sCT) + 0.0005N HCl + 0.85% NaCl

II 4x25 µl " + " +0.27% NaP + 0.04% PNP + 0.83% NaCl

III 4x25 µl " + " +0.2% βEtOH + 0.5% BzOH + 0.1% Tween 80 + 0.85% NaCl

IV 4x25 µl " + " + " +1% BzOH + " + "

* other formulation experiment on BA 311–312

NOTEBOOK # [illegible]
PAGE # 15
DATE 6/25/99
INITIALS [illegible]

EXHIBIT C

Title: HPLC 8/13/99

(1)

7/30/99 Effect of buffer concentration on DCT stability in liquids

005: citric acid + 9.61 g dissolved in 80ml H_2O, adjusted pH to 3.7 with 2N NaOH, dil to 100ml

lot# [illegible] DCT 52% peptide + 0.1454 g 119.2mg for 10mg/ml add 11.9ml H_2O

Row	1	2	3	4	5	6	7	8	9	
16–18		final conc mM CITRATE pH 3.7	500mM CITRATE pH 3.7 ml	DCT 10mg/ml ml	% pluronic, 1% Brij, 1% [illegible] ml	% Benzalkonium 1% NaCl ml	H_2O ml	pH	1N HCl	
19	7/30/99 -1	1	.01	0.1	2.5		2.39	4.22		tossed
20	-2	10	.1	↓	↓		2.3	3.88		
21	-3	25	.25				2.15	3.81		
22	-4	50	.5				1.9	3.81		
23	-5	100	1				1.4	3.83		
24	-6	1	.01	0.1		2.5	2.39	4.19		tossed
26	-1			.1ml	2.5ml		2.4ml	4.35	1ul	tossed
27	-6			.1ml		2.5ml	2.4ml	5.18	1ul	↓
28	-1								1ul	tossed
29	-6								3	
30	-1			.1ml	2.5ml		2.4ml	5.18		kept
31	-6			.1ml		2.5ml	2.4ml	5.13		kept

→ see next page for addition of HCl & adjust pH

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[illegible] 8/13/99

EFFICIENCY LINE® 22-208

Title: HPLC

8/13/95

(2)

1	2 1N NaOH ml	3 pH	4 conc HCl	5 pH	6	7	8	9
1	1	4.2						
2	1	3.84						
3	6	3.79						
4			1	3.81				
5			3	3.75				
6	1	4.13						
1	1	3.65						
2	2	3.76						
3	4	3.74						
4			1	3.78				
5								
6	1	3.6						
1								
2	1	3.74						
3								
4								
5								
6								

NOTEBOOK # LMF-95-030
PAGE # 206
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INITIALS LMF

EFFICIENCY LINE® 22-206

EXHIBIT D

Stability Studies on Unigene's Candidate sCT Nasal Formulations

Date: January 27, 1999

Preparation of sCT Stock Solution (for the preparation #1, #2, #3, #4, #5, #6, #7, and #8 candidate nasal formulations):

0.6836* g sCT (Lot # 1100-6010, % peptide = 83%, Exp. 8/1998) was dissolved in 100 mL of purified water (Fairfield Drop 1). The solution (i.e., conc.=567.4 mg/mL) was kept at 4 °C until use.

Preparation Date: January 27, 1999, stored at 4 °C, prepared by ETM, expires on January 27, 2000

ETM 1-27-99 *Please page 51 for the printout

Target Compositions of Experimental Candidate Nasal Formulations: ETM 1-29-99

The following are the target compositions of the various experimental formulations:

Formulation #	Target pH	sCT (ug/mL)	Citric Acid (mM)	NaCl (mM)	Tween 80 (0.1g/100mL)	Benzyl Alcohol (0.1g/100mL)
1	N/A	560	-	128	-	-
2	N/A	560	-	128	Yes	Yes
3	3.30	560	10	128	-	-
4	3.30	560	10	128	Yes	Yes
5	3.70	560	10	128	-	-
6	3.70	560	10	128	Yes	Yes
7	4.10	560	10	128	-	-
8	4.10	560	10	128	Yes	Yes
9	4.50	560	10	128	-	-
10	4.50	560	10	128	Yes	Yes
11	3.30	560	100	128	-	-
12	3.30	560	100	128	Yes	Yes
13	3.70	560	100	128	-	-
14	3.70	560	100	128	Yes	Yes
15	4.10	560	100	128	-	-
16	4.10	560	100	128	Yes	Yes
17	4.50	560	100	128	-	-
18	4.50	560	100	128	Yes	Yes

REFERENCE ETM 1-29-99 NOTE BOOK # 0415 PAGE #

Note: The target compositions of the various experimental nasal formulations were provided to me by Dr. Bill Stern of Unigene Laboratories, Inc. at Fairfield.

ETM 1-27-0

Stability Studies of sCT Nasal Candidates

ASSOC: EM-002
DATE: 3/12/99
PAGE #: 182
NAME: EM

RESULTS/DISCUSSION:

Summary of Stability Results of Possible Unigene Nasal Product

① Form. #9 appears to be least stable at 4°C after 1 mo. (~77% of active ingredient remaining after 1 month).

② Form. #9 is least stable after 1 month at 25°C.

Form. #	Target pH	Actual Final pH	% Remaining after 3 days at 4 °C	% Remaining after 7 days at 4 °C	% Remaining after 14 days at 4 °C	% Remaining after 1 mo. at 4 °C	% Remaining after 3 days at 25 °C	% Remaining after 7 days at 25 °C	% Remaining after 14 days at 25 °C	% Remaining after 1 mo. at 25 °C
1	n/a	5.03	99.3%	102.5%	103.6%	104.1%	99.7%	98.2%	97.3%	97.6%
2	n/a	5.02	98.7%	102.6%	101.6%	102.9%	97.5%	96.3%	95.7%	97.4%
3	3.30	3.27	99.9%	101.5%	102.2%	103.6%	99.3%	100.1%	101.0%	100.3%
4	3.30	3.36	101.0%	101.1%	101.9%	102.6%	100.4%	101.0%	101.5%	101.1%
5	3.70	3.70	100.1%	101.5%	102.8%	102.5%	98.8%	99.2%	101.4%	98.8%
6	3.70	3.70	99.1%	101.1%	101.6%	101.2%	99.7%	98.1%	101.2%	99.6%
7	4.10	4.15	99.3%	100.6%	101.3%	100.6%	98.6%	100.1%	98.7%	99.1%
8	4.10	4.11	99.5%	100.8%	100.9%	100.7%	100.3%	99.8%	100.0%	99.6%
9	4.50	4.50	97.5%	98.2%	98.4%	76.6%	95.7%	94.9%	94.6%	68.7%
10	4.50	4.54	102.5%	102.7%	102.6%	101.9%	102.0%	101.7%	100.5%	97.7%
11	3.30	3.30	102.9%	102.1%	101.6%	100.2%	102.7%	101.4%	102.4%	98.3%
12	3.30	3.31	102.5%	102.4%	101.1%	102.1%	102.3%	101.6%	101.5%	97.9%
13	3.70	3.70	102.2%	99.7%	101.1%	100.7%	100.1%	100.7%	98.7%	97.2%
14	3.70	3.76	100.8%	101.1%	98.0%	100.5%	100.3%	100.0%	99.5%	97.5%
15	4.10	4.17	101.5%	101.6%	101.4%	99.3%	101.2%	100.3%	99.8%	95.4%
16	4.10	4.10	100.3%	99.7%	100.5%	99.8%	100.3%	99.3%	98.7%	94.7%
17	4.50	4.48	101.7%	99.8%	101.2%	86.8%	101.2%	100.2%	98.7%	74.3%
18	4.50	4.50	98.8%	100.0%	99.2%	100.3%	99.9%	99.6%	98.0%	94.0%

EM
3-12-99

Note: % Recovery was calculated by getting the ratio of the sCT peak area at any time > 0h to that at time = 0h for a particular formulation

Stability Studies of sCT
Nasal Candidates

ETM: 002
DATE 3/12/99
PAGE # 183
NAME ETM: cont.

RESULTS / DISCUSSION:

Summary of Stability Results of Possible Unigene Nasal Product

(1.) Form. #17 is least stable after ~1 mo. at 25°C.

(2.) Form. #3, #4, #5, ~#6 are the most stable after 1 month at 50°C.

Form. #	Target pH	Final pH	% Remaining after 3 days at 37 °C	% Remaining after 7 days at 37 °C	% Remaining after 14 days at 37 °C	% Remaining after 1 mo. at 37 °C	% Remaining after 3 days at 50 °C	% Remaining after 7 days at 50 °C	% Remaining after 14 days at 50 °C	% Remaining after 1 mo. at 50 °C
1	n/a	5.03	98.6%	93.8%	83.4%	62.6%	78.9%	62.0%	44.9%	15.6%
2	n/a	5.02	97.4%	91.3%	85.0%	66.1%	77.6%	61.1%	47.2%	11.3%
3	3.30	3.27	99.5%	100.6%	98.2%	94.7%	95.9%	95.9%	82.2%	74.9%
4	3.30	3.38	99.8%	99.3%	98.8%	94.7%	96.8%	93.0%	86.9%	88.9%
5	3.70	3.70	97.9%	99.4%	97.6%	93.4%	96.5%	92.6%	84.3%	83.3%
6	3.70	3.70	99.3%	99.4%	96.9%	92.4%	95.5%	91.5%	82.8%	83.1%
7	4.10	4.15	99.9%	97.4%	96.2%	88.7%	92.0%	84.9%	73.6%	47.9%
8	4.10	4.11	99.5%	97.1%	92.8%	89.2%	92.8%	87.2%	74.3%	52.0%
9	4.50	4.50	92.6%	89.1%	82.6%	69.3%	75.3%	60.6%	41.7%	19.1%
10	4.50	4.54	98.6%	95.4%	88.9%	76.8%	84.7%	65.6%	45.3%	21.9%
11	3.30	3.30	98.5%	94.5%	90.6%	82.0%	90.7%	77.1%	61.2%	40.6%
12	3.30	3.31	100.0%	97.0%	91.2%	81.7%	88.9%	70.0%	60.9%	39.6%
13	3.70	3.70	98.7%	94.3%	91.3%	80.0%	87.1%	68.7%	54.1%	31.5%
14	3.70	3.78	97.9%	93.7%	90.3%	78.3%	87.6%	71.3%	54.4%	31.6%
15	4.10	4.17	98.7%	93.8%	87.3%	74.1%	83.8%	63.8%	41.1%	21.1%
16	4.10	4.10	98.9%	93.4%	87.0%	74.0%	83.1%	64.9%	46.8%	22.9%
17	4.50	4.48	96.8%	87.9%	73.2%	39.8%	77.8%	54.0%	34.8%	14.3%
18	4.50	4.50	97.0%	90.5%	83.6%	57.3%	78.0%	48.9%	32.9%	8.4%

ETM
3-12-99

Note: % Recovery was calculated by getting the ratio of the sCT peak area at any time > 0h to that at time = 0h for a particular formulation

WITNESSED BY: